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Impaired local dynamic stability during treadmill walking predicts future falls in patients with multiple sclerosis: A prospective cohort study

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ABSTRACT

Background: Falling is a significant problem in patients with multiple sclerosis (MS) and the majority of falls occur during dynamic activities. Recently, there have been evidences focusing on falls and local stability of walking based on dynamic system theory in the elderly as well as patients with cerebral concussion. However, in patient with MS, this relationship has not been fully investigated. The aim of this study was to investigate local stability of walking as a risk factor for falling in patients with MS.
Methods: Seventy patients were assessed while walking at their preferred speed on a treadmill under single and dual task conditions. A cognitive task (backward counting) was used to assess the importance of dual tasking to fall risk. Trunk kinematics were collected using a cluster marker over the level of T_7 and a 7-camera motion capture system. To quantify local stability of walking, maximal finite-time Lyapunov exponent was calculated from a 12-dimensional state space reconstruction based on 3-dimensional trunk linear and angular velocity time series. Participants were classified as fallers (≥ 1) and non-fallers based on their prospective fall occurrence.
Findings: 30 (43%) participants recorded ≥ 1 falls and were classified as fallers. The results of multiple logistic regression analysis revealed that short-term local dynamic stability in the single task condition ($P < 0.05$, odds ratio = 2.214 (1.037–4.726)) was the significant fall predictor.
Interpretation: The results may indicate that the assessment of local stability of walking can identify patients who would benefit from gait retraining and fall prevention programs.

1. Introduction

Falling represents a serious risk for patients with multiple sclerosis (PwMS); > 50% of patients have a history of at least one fall over a 6-month period (Gunn et al., 2013a; Kasser et al., 2011). To date, several risk factors for falling such as worse disability level, progressive type of disease, use of walking aids, impaired cognition, reduced walking speed and poorer balance performance have been identified in PwMS (Cattaneo et al., 2002; Gunn et al., 2013b; Nilsagard et al., 2009). Among those potentially modifiable risk factors, impaired walking has a high prevalence i.e., approximately 85% of patients with MS report gait disturbances as their main complaint (Bethoux and Bennett, 2011; Sosnoff et al., 2011; Tajali et al., 2017). Given the high frequency of falls and the incidence of fall-related injuries in PwMS, an early detection of mobility-related risk factors for falling is critical to allow timely interventions and to prevent the occurrence of recurrent falls in these patients.

Recently, there has been an increasing recognition that investigation of local dynamic stability (LDS) based on nonlinear dynamics can provide a deeper insight regarding the locomotor control and fall risk (Bruijn et al., 2013; Lockhart and Liu, 2008; Peebles et al., 2017). While traditional linear measures such as the range, standard deviation, and coefficient of variation of the time series provide information on the magnitude of variability within the system, nonlinear measures provide information on the temporal structure of the time series and variations of gait patterns over time (Dingwell et al., 2001; Dingwell and Marin, 2006; Stergiou and Decker, 2011). LDS can be assessed during normal walking using maximal finite-time Lyapunov Exponents (LyE) which quantify the rate of divergence between neighboring trajectories in a reconstructed state-space of the system's dynamic (Bruijn et al., 2009;

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Bruijn et al., 2010; Bruijn et al., 2013) The results of previous studies have revealed that measures of kinematic variability are not well correlated with measures of LDS that directly quantify the sensitivity of gait to small perturbations such as floor irregularities (Dingwell et al., 2001; Dingwell and Cavanagh, 2001).

Regarding the clinical application of LDS measures, it has been shown that LDS of walking is a more responsive index to show the effects of a gait training program in PwMS than other gait performance tests such as 10-meter walk, 3-minute walk and step frequency (Hilfiker et al., 2013). However, its ability to predict falls has not been fully investigated in PwMS. A study on the neurological patients with the paresis of the lower extremity including MS, stroke, traumatic brain and spinal cord injury patients showed that LyE discriminated well between patients with a low walking ability and healthy controls (Reynard et al., 2014). Nevertheless, the majority of these studies relied on retrospective or cross-sectional designs and the predictive value of LDS to identify fall risk has not yet been confirmed in PwMS (Lockhart and Liu, 2008; Peebles et al., 2017; Reynard et al., 2014; Toebes et al., 2012). This issue is of great importance since prospective models of fall assessment identify the rate of falling in a certain time period in future, thereby identifying possible cause and effect relationship (Coote et al., 2014). In contrast, retrospective or cross sectional studies only reveal some kind of relationship between a number of factors and fall history.

In addition to the gait problems commonly reported by PwMS (Bethoux and Bennett, 2011; Comber et al., 2016), cognitive impairments are also experienced by 65% of PwMS (Gianni et al., 2014; Gunn et al., 2013a). Although there are a number of studies which have investigated the effects of dual tasking on LDS of walking in various populations (Fino, 2016; Lamoth et al., 2011; van Schooten et al., 2016), no studies have yet investigated the association between dual task tests of LDS and fall risk in PwMS. In the elderly, the results of a previous study revealed that LDS of walking decreased under a cognitive dual task condition (Lamoth et al., 2011). Moreover, the results of a recent study in the cerebral concussed patients demonstrated a significant decrease in the LyE under a cognitive dual task condition (Fino, 2016). However, none of these studies investigated the predictive ability of LDS measures under dual task conditions. This issue is important since walking in the real world requires paying attention to various environmental features and at the same time recovering from perturbations to avoid falls. Therefore, the purpose of the current study was to prospectively assess the predictive ability of LDS of walking and its dual task costs (DTCs) to identify fall risk in PwMS. Based on the current available evidences (Learmonth et al., 2016; Mofateh et al., 2017; Tajali et al., 2017; Wajda and Sosnoff, 2015), it was hypothesized that LyE and their dual task costs (DTCs) can predict future falls in PwMS. Information obtained from this study will help clinicians to prescribe fall treatment and prevention programs based on the underlying gait deficits in the single or dual task conditions.

2. Methods

2.1. Participants

Seventy PwMS were recruited from the Khuzestan MS Patients' Society. Inclusion criteria were as follow: (2) a definite diagnosis of MS (of any subtype) as diagnosed by a neurologist, (2) an expanded disability status scale (EDSS, physician version) of 0 to 5.5, (3) no MS relapses 30 days prior to testing, and (4) the ability to walk independently for at least 2-min on a treadmill. Individuals who stopped repeatedly were excluded since a correct LDS assessment requires a minimal number of 85 consecutive gait cycles (Bruijn et al., 2013; Riva et al., 2014). Each participant signed an inform consent form that had been approved by the Internal Review Board of the University. Age, gender and the self-administered EDSS score for disease severity and other patients' characteristics are reported in Table 1.

Table 1
Demographic and clinical characteristics of non-faller and faller groups.

Characteristics		Non-fallers	Fallers	*P*-value
Number of participants (%)		40 (57%)	30 (43%)	NA
Age (yr)		33.12 (8.05)	35.48 (9.71)	0.29
Gender (female/male)		34/6	15/15	< 0.01
BMI (kg/m^2)		26.21 (5.34)	23.76 (2.98)	< 0.05
Disease duration (yr)		3.78 (4.00)	5.48 (5.38)	0.13
EDSS$_S$		3.15 (0.96)	4.18 (0.56)	< 0.01
Gait speed		1.80 (0.31)	1.68 (0.27)	0.11
Type of MS	Relapsing-remitting	40	26	0.11
	Secondary progressive	0	4	
	Primary progressive	0	0	

Note. Values are mean (standard deviation) or as otherwise indicated. EDSS$_S$: self-administered expanded disability status scale. NA: not applicable.

2.2. Procedures

Participants were assessed under the 2 experimental conditions, each lasting for 2-min: (1) single-task walking, (2) dual-task walking. Kinematic data were collected using a 7-camera motion capture system (Qualisys Inc., Sweden) at a sampling rate of 100 samples/s. Spherical retro-reflective markers, 10 mm in diameter, were attached to the heels bilaterally to calculate heel strike events. Moreover, a cluster of 3 infrared retro-reflective markers was placed over the level of T_7 to calculate LDS (Bruijn et al., 2010; Bruijn et al., 2013). This location was chosen based on the fact that maintaining stability of the trunk is a critical aspect of locomotion (Bruijn et al., 2013).

For the single-task walking condition, patients were instructed to walk straight ahead, while barefoot, at a self-selected comfortable walking speed on a motorized treadmill (Biometrix, length: 1.5 m, width: 0.5 m). Handrails of the treadmill were removed. To provide safety during walking, a harness was suspended from the ceiling and was loosely fixed around the waist of each participant. For the dual-task condition, participants were instructed to walk while counting backward aloud by 3 from a randomly selected number between 200 and 300. The conditions were randomly selected and a rest period of 5 min was given to prevent fatigue effects.

Subjects were tested at their self-selected walking speed during the experiment. To get familiarized with the treadmill walking and also obtain the preferred speed, participants were asked to walk for 5 min before commencing the test procedure. They were asked to walk on the treadmill commencing at 0.8 km/h, gradually increasing the speed by 0.1 km/h until they report their preferred speed (Mofateh et al., 2017). The speed of the treadmill was again increased and decreased in 0.1 km/h intervals to reconfirm the preferred speed (Mofateh et al., 2017). Participants were given enough rest before the actual experiment.

2.3. Data analysis

Maximum LyE were calculated to quantify LDS in this study (Bruijn et al., 2010). Firstly, trunk position data were filtered by a 4th order zero-lag Butterworth low pass filter with the cut off frequency of 20 Hz. Then, trunk linear velocities were obtained by differentiating the average position of trunk cluster markers while angular velocities of the trunk were calculated using the Euler method (Siciliano and Khatib, 2016). All analyses were performed on the velocity time series to minimize the effects of non-stationarity in the position data.

Then, using a spline interpolation, linear and angular velocity time series of each trial were time normalized to $n \times 100$ (n = number of strides) so that each stride approximately consisted of 100 samples. This issue is important since LyE algorithm is sensitive to both the number of data samples and the number of gait cycles (Bruijn et al., 2010). Heel strike events were determined when the sign of heel marker anteroposterior (AP) velocity changed. To reconstruct the state-space, the maximum available number of strides across all subjects was selected so that each state space consisted of exactly the same number of samples. The dimension of the state-space was 12 including linear, angular velocities and their delayed copies. Since after the time normalization, time series contained the same number of samples and the same base frequencies, a fixed time delay of 25 samples was used so that it represents a 90-degree phase shift equivalent to a derivative. Then, short (λ_s) and long (λ_l) time LyE were calculated from the reconstructed state-space using Rosenstein's algorithm. After that, the nearest neighbors were identified for each point and the distances between trajectories were determined as a function of time. The divergence curves were calculated from the reconstructed state-space and the average of the logarithm of the divergence curves was determined. From this curve, λ_s and λ_l were identified as the linear slopes over the duration of one step and one stride respectively (Reynard et al., 2014).

Furthermore, in order to estimate cognitive motor interference, we calculated dual-task cost (DTC) for λ_s and λ_l.

$$DTC = 100\left(\frac{S-D}{S}\right)$$

where S equals single-task performance and D is equal to dual-task performance for each parameter.

2.4. Follow-up assessment of falls

In contrast to retrospective approach of fall assessment which questions on the number of falls experienced several months before testing and may be subjected to recall bias, prospective approach measures the rate of falling in a certain time period after the initial assessment (Coote et al., 2014; Gianni et al., 2014; Nilsagard et al., 2009). Therefore, we define a time period of 6 months and follow-up the rate of falling in this period. For this purpose, subjects were asked to record their falls on the fall calendars and return these calendars at the end of each month. In addition, they were contacted during the first week of the fall count to remind them to count their falls.

For the purpose of patients' monitoring, research assistants telephoned each patient every 6 weeks, on average, to follow up each individual's fall data. A fall was defined as an unexpected event that results in ending up on the ground, floor, or any lower surface (Coote et al., 2014; Tajali et al., 2017). Based on the previous studies, patients were classified as fallers if they had reported one or more falls during the 6-month follow up period (Gianni et al., 2014; Tajali et al., 2017).

2.5. Statistical analysis

Firstly, univariate logistic regression analysis was conducted to determine the predictive ability of each variable separately. Then, variables with a $P < 0.1$ were entered into multiple logistic regression analysis adjusted by the demographic and clinical variables. Odds ratios (OR) and 95% confidence intervals (CI) were calculated for each regression analysis. Furthermore, in order to have a comprehensive assessment of the two patient groups, a series of independent *t*-tests were done to allow between group comparisons of fallers and non-fallers on all outcome measures of this study. All analyses were conducted using the IBM SPSS statistics software (Version 22). Significance level was set at $P < 0.05$.

3. Results

3.1. Participants and fall data

Approximately 43% of participants (30 patients) reported 1 or more falls during the 6-month follow-up period. Table 1 summarizes participants' characteristics including clinical and demographic data for the two patient groups (non-fallers and fallers). The results of a series of independent *t*-tests revealed that there were significant differences in the $EDSS_S$, BMI and gender between fallers and non-fallers (Table 1).

The results of the univariate logistic regression models revealed that λ_s under both the single and dual-task conditions and λ_l under the single task condition were the significant fall predictors in PwMS, while DTC of λ_s and λ_l were not significant predictors (Table 2). Since there were significant differences between fallers and non-fallers regarding disability, gender and BMI, we conducted multiple regression analysis and adjusted the effects of these variables. The results of multiple regression analysis revealed that only λ_s was the significant fall predictor i.e. the odds of falling was 2.21 times greater with 1 standard deviation (SD) increase in the λ_s (Table 3). In addition, the results of series of independent *t*-tests revealed that fallers had greater instability in walking, as determined by λ_s, λ_l and cognitive λ_s, than non-fallers at the time of assessment (Table 4).

Table 2
Univariate logistic regression analysis with fall incidence (no fall versus ≥1 fall) as the dependent variable.

Predictors	B	SE	Wald	df	*P*-value	Odds ratio (95% confidence interval)
λ_s	0.903	0.294	9.419	1	0.002	2.466 (1.386–4.389)
λ_l	0.638	0.271	5.548	1	0.018	1.893 (1.113–3.219)
Cognitive λ_s	0.524	0.265	3.925	1	0.048	1.689 (1.006–2.837)
Cognitive λ_l	0.315	0.249	1.606	1	0.205	1.370 (0.842–2.231)
DTC λ_s	0.284	0.259	1.208	1	0.272	1.329 (0.800–2.206)
DTC λ_l	0.345	0.277	1.552	1	0.213	1.412 (0.821–2.429)

λ_S: Lyapunov exponent (LyE) over the duration of one step, λ_l: LyE over the duration of one stride, cognitive λ_s: LyE in the dual task condition over the duration of one step, DTC: dual task cost, B: regression coefficient; SE: standard error; df: degrees of freedom; adjusted OR: odds ratio; CI: confidence interval.

4. Discussion

In the present study, we investigated the predictive ability of LDS for future fall identification in a sample of PwMS, who were ambulatory independent. In our sample, 43% of participants experienced at least one fall over the 6-month follow-up period and were classified as fallers. The results of the logistic regression analysis, after adjusting for clinical and demographic variables, revealed that short-term LyE (λ_s) under the single-task condition was the significant fall predictor in PwMS. i.e. reduced LDS of walking at the time of assessment was predictive of future falls. This finding is novel and significant as this was the first prospective study that investigated the predictive ability of a non-linear measure of gait stability (LyE) in PwMS. Although both groups of fallers and non-fallers were ambulatory with mild-to-moderate disease severity (EDSS < 6) and had similar ages and disease duration, they had distinct levels of gait LDS which may provide an insight into a mobility-related factor associated with falling in these patients. This finding supports the results of previous studies in the healthy elderly which demonstrated that LyE may be a valid predictor of falling (Lockhart and Liu, 2008; Toebes et al., 2012; van Schooten

Table 3
Multiple logistic regression with fall incidence (no fall versus ≥1 fall) as the dependent variable.

Predictors	B	SE	Wald	df	*P*-value	Odds ratio (95% confidence interval)
λ_s	0.795	0.387	4.222	1	< 0.05	2.214 (1.037–4.726)
λ_l	0.506	0.352	2.074	1	0.150	1.659 (0.833–3.304)
Cognitive λ_s	0.432	0.319	1.830	1	0.176	1.540 (0.824–2.877)

Adjusted for BMI, gender and $EDSS_S$, λ_s: Lyapunov exponent (LyE) over the duration of one step, λ_l: LyE over the duration of one stride, cognitive λ_s: LyE in the dual task condition over the duration of one step, B: regression coefficient; SE: standard error; df: degrees of freedom; OR: odds ratio; CI: confidence interval.

Table 4-
Results of independent T-tests between faller and non-faller groups.

Variables	Non-fallers Mean (SD) (n = 40)	Fallers Mean (SD) (n = 30)	*P*-value Mean differences
λ_s	0.537 (0.133)	0.668 (0.177)	0.001
λ_l	0.332 (0.108)	0.407 (0.107)	0.013
Cognitive λ_s	0.521 (0.139)	0.600 (0.176)	0.041
Cognitive λ_l	0.342 (0.142)	0.385 (0.130)	0.204
DTC λ_s	0.009 (0.200)	0.059 (0.162)	0.272
DTC λ_s	−0.051 (0.358)	0.039 (0.177)	0.207

λ_s: Lyapunov exponent (LyE) over the duration of one step, λ_l: LyE over the duration of one stride, cognitive λ_s: LyE in the dual task condition over the duration of one step; DTC: dual task cost.

et al., 2016).

There is an increasing evidence that LDS could be used as a pertinent bio-marker for identifying various diseases and adverse conditions such as falling and disability (Reynard et al., 2014; Stergiou and Decker, 2011; Toebes et al., 2012). Consistent with this hypothesis, in a cross sectional study, Huisinga et al., found that trunk control during walking was impaired in PwMS in comparison to the healthy subjects suggesting that improving trunk stability should be considered as a goal in the balance rehabilitation protocols (Huisinga et al., 2013). Furthermore, Peebles et al. found differences in the LDS between PwMS who had a previous fall history and those who had no fall history (Peebles et al., 2017). Although the results obtained in the aforementioned study are valuable in terms of investigating a series of nonlinear and linear gait variability and stability measures in PwMS (Peebles et al., 2017), they relied on retrospective fall assessment and the predictive values of these parameters to identify fall risk remained unknown. Another noteworthy study by van Schooten et al. illustrated that daily life gait characteristics including LDS were predictive of future falls in the elderly (van Schooten et al., 2016). In contrast to our study, they used a single trunk accelerometer and analyzed a series of motor control characteristics including gait stability, variability, smoothness and symmetry in the older adults (van Schooten et al., 2016). Taken together, these findings revealed that investigation of parameters related to locomotor control may be a promising approach to identify patients who require gait retraining in their fall prevention programs (Hilfiker et al., 2013; van Schooten et al., 2016).

Among the variables investigated in this study, the LDS measures in the dual-task condition and their DTCs were not predictive of the future falls in PwMS. Although there was significant between-group differences in the dual-task test variables, in terms of prediction and after the adjustment of disability, gender, and BMI; these variable did not yield to a significant prediction. Regarding the predictive validity of DTC of laboratory gait measures, only the DTC of traditional gait parameters including gait speed and stride length were investigated previously in PwMS (Etemadi, 2016). In a study by Etemadi, gait was assessed through an electronic walkway and only the DTC of walking speed was found to be predictive of the future falls in PwMS (Etemadi, 2016). Regarding other patient's populations, in a longitudinal study by Fino, the effect of dual taking on the LDS of walking was assessed in 5 patients with cerebral concussion (Fino, 2016). The results revealed a significant decrease in the LDS and an increase in stride time variability during dual-task walking despite similar single-task stability and variability with healthy controls (Fino, 2016). However, in this study no association between DTC of LDS and falling was investigated. Overall, the controversy obtained in the results of our study with previous studies regarding dual tasking may be due to differences in the study design, study variables, experimental conditions (over ground versus treadmill walking) or the level of cognitive task difficulty used in the previous experiments.. Maybe, the use of more attentional demanding tasks (serial seven subtraction) in the more challenging environments (narrow-based walking) may provide additional insight into the effects of dual-tasking on the fall prediction in PwMS.

From a methodological perspective, we measured long-term LDS in a shorter time interval (one stride versus 4–10 stride). The logic behind this analysis was the fact that previous studies that measured λ_l in 4–10 stride did not reveal any sensitivity or between- group differences for this variable (Dingwell et al., 2001; Dingwell and Marin, 2006). We hypothesized that this may be due to the fact that λ_l is measured in an interval where most divergence is damped down due to either explicit control and/or the attractor size limitations (physiological or anatomical constraints). In fact, we again found a predictive ability only for the short-term LDS not the long-term. Therefore, short- term LDS seems to be a more valid indicator to estimate the probability of falling in PwMS (Bruijn et al., 2010).

Although this study highlighted an association between a decreased dynamic stability and an increased fall risk in PwMS, several limitations are needed to be considered. Firstly, the fall incidence in our sample was less than what is commonly reported in the literature (< 50%) (Gianni et al., 2014; Gunn et al., 2013a), which may affect the results of this study. Secondly, the method of this study cannot be applied to very poor walkers and hence the applicability is limited to a subset of patients with an independent walking ability. Furthermore, patients of this study were assessed with a laboratory-based set-up including a motion analysis system and a treadmill. The use of wireless trunk accelerometers during over ground walking in daily life may enhance the assessment of LDS in the real life situations or in the clinical settings (van Schooten et al., 2016). In addition, they seem to be more time efficient than laboratory-based measurements. Future studies shall utilize three dimensional trunk accelerometers to investigate the predictive validity of a series of nonlinear measures, combined with subjective measures (Tajali et al., 2017), in a larger sample of MS patients to develop an optimal model to predict the fall risks associated with walking.

5. Conclusion

In conclusion, this study supports using the LDS to predict the probability of falling in PwMS, thereby incorporating it into the fall risk assessments and fall prediction models. As the reduced ability to respond effectively to intrinsic or small extrinsic perturbations during walking can predispose patients to larger perturbations and to falling (Pai et al., 2014a), investigation of the effects of perturbation-based gait rehabilitation programs on the rate of falling is recommended in these patients (Pai et al., 2014b).This issue is important as the results of previous studies revealed that traditional fall prevention programs including stretching, strengthening, yoga and balance training were not effective in reducing the rate of future falling in PwMS (Gunn et al., 2015).

Declaration of Competing Interest

None of the authors had any financial or other interests relating to the manuscript to be submitted for publication in the journal of clinical biomechanics.

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